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Abstract: Background: Antiangiogenic treatment has been explored in few patients with hemangioblastoma after failure of surgery and radiotherapy. Case Report: We present the first histopathological follow-up study of a bevacizumab-responsive hemangioblastoma that eventually progressed. For a period of 12 months, therapy with bevacizumab achieved a clinical response and radiological stabilization in a patient with progressive multifocal central nervous system (CNS) hemangioblastoma. Subsequently, selected tumor sites showed radiological progression, in particular, the formation of an intramedullary lesion of the initially predominantly leptomeningeal disease. Histology showed diffuse dural invasion by the hemangioblastoma accompanied with a relatively reduced cell density compared to the preserved vessel structures. Conclusion: The pattern of progression upon vascular endothelial growth factor (VEGF)-targeting antiangiogenic treatment in hemangioblastoma may involve increased tumor invasiveness.

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Neuropathological Characteristics of Progression after Prolonged Response to Bevacizumab in Multifocal Hemangioblastoma

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Established Facts

– Based on previous case studies, antiangiogenic treatment with bevacizumab represents a therapeutic option in patients with progressive and heavily pretreated hemangioblastoma.

Novel Insights

– This is the first study presenting the patterns of progression in a patient with multifocal hemangioblastoma after prolonged response to bevacizumab.
– Radiological and histopathological findings point towards an increased tumor invasiveness on the basis of relatively reduced tumor cell density in contrast to a preserved vasculature.

Keywords

Bevacizumab · VEGF · Hemangioblastoma · Angiogenesis

Summary

Background: Antiangiogenic treatment has been explored in few patients with hemangioblastoma after failure of surgery and radiotherapy. **Case Report:** We present the first histopathological follow-up study of a bevacizumab-responsive hemangioblastoma that eventually progressed. For a period of 12 months, therapy with bevacizumab achieved a clinical response and radiological stabilization in a patient with progressive multifocal central nervous system (CNS) hemangioblastoma. Subsequently, selected tumor sites showed radiological progression, in particular, the formation of an intramedullary lesion of the initially predominantly leptomeningeal disease. Histology showed diffuse dural invasion by the hemangioblastoma accompanied with a relatively reduced cell density compared to the preserved vessel structures. **Conclusion:** The pattern of progression upon vascular endothelial growth factor (VEGF)-targeting antiangiogenic treatment in hemangioblastoma may involve increased tumor invasiveness.

Introduction

Hemangioblastoma represents a rare tumor of the central nervous system (CNS) occurring both as sporadic disease and, especially in case of a spinal manifestation, in association with von Hippel-Lindau (VHL) disease [1]. The tumor cell of origin and the histogenesis of this entity remain controversial. The disease-associated inactivation of the VHL tumor suppressor gene leads to a stabilization of the hypoxia-inducible factor (HIF)-1α protein and thereby to an up-regulation of associated target genes, including the gene coding for the vascular endothelial growth factor (VEGF) [2]. Hemangioblastomas are mostly encountered in the cerebellum and dorsal spinal cord, where they are usually superficial, centered on the pial surface and well circumscribed. 2 histopathologic subtypes related to tumor size are recognized, including the smaller 'reticular or mesenchymal type' with a high ratio of vessels to tumor cells and the less common 'cellular type' composed of large lobules of uniform cells surrounded by proliferating vessels [3]. In addition, the constituent tumor (stromal) cells of the reticular variant often show abundant vacuolated cytoplasm and are embedded in a dense reticulin network. The cellular variant shows less cytoplasmic vacuolation, sparse

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pericellular reticulin and, in some cases, glioma-like fibrillar areas. Since VEGF and VEGF receptors (VEGFRs) are expressed in hemangioblastoma [4, 5], antiangiogenic therapy is now being considered as a therapeutic option beyond surgery and radiotherapy. To date, few cases of progressive hemangioblastoma treated successfully with the VEGF antibody bevacizumab have been published [6, 7]. In a single-arm phase II study with the VEGFR inhibitor sunitinib in patients with VHL disease, stable disease was reported in 9/11 patients with hemangioblastoma while 6/18 patients with other VHL-related lesions showed a partial response [8]. To better understand the patterns of response and therapeutic alterations, tissue analyses of patients before and after antiangiogenic therapy are highly desirable.

Patient and Methods

The patient, specifically his response to bevacizumab with a follow-up of 4 months, was reported previously [6]. After written informed consent from the patient, treatment with bevacizumab at 10 mg/kg was administered intravenously every 14–21 days on the basis of compassionate use of the drug. Radiographic follow-up analyses were performed with 1.5-Tesla magnetic resonance imaging (MRI) according to standard procedures. The tissue specimen from the surgery before treatment with bevacizumab consisted of a 0.4 × 0.2 × 0.01 cm soft, red-brown tissue fragment. At progression after bevacizumab, the tissue comprised multiple beige fragments measuring 8 × 7 × 2 mm in aggregate.

Case Report

Clinical and Radiological Course

A 70-year-old man with a history of a solitary left cerebellar hemangioblastoma resected in 1994 was diagnosed with local tumor recurrence in 2009 and multiple leptomeningeal cerebral and spinal lesions in 2010. No other lesions suggestive of VHL disease were found, and no germ-line mutation was identified upon analysis of exons 1–3 of the VHL gene. After rapid radiological and clinical progression, experimental treatment with bevacizumab was initiated. The clinical course up to 4 months after start of treatment was described previously [6]. In brief, upon initiation of bevacizumab treatment, the patient's gait disorder and performance status improved remarkably and the formerly progressive lesions on imaging (fig. 1A, B) showed stable disease in the first follow-up after 2 months. The patient was maintained on bevacizumab, and MRI imaging showed sustained stable disease up to 12 months after start of therapy (fig. 1C). 3 months later, however, routine MRI scans revealed an intramedullary contrast-enhancing lesion, which showed further progression in the subsequent follow-up scan (fig. 1D, right). Later, progression of the extramedullary, intradural cystic lesions was found near the spinal cord at the levels of C7 and T11 (fig. 1D, left). In line with the radiological course, ambulation difficulty was documented on examination. Another surgery was performed in order to prevent further compression of the spinal cord. Intraoperatively, the lower dorsal lesion appeared superficially infiltrative but exophytic and was completely resected. However, the upper lesion was ventrally incorporated in the spinal cord and therefore only biopsy could be safely performed to spare the motor tracts. The next follow-up scans showed further tumor progression of the spinal lesions, warranting further treatment with limited evidence-based options.

Histologic Analysis

The initial diagnosis of hemangioblastoma World Health Organization (WHO) grade I was rendered based on cerebellar lesions, and multilocular disease was confirmed by a biopsy of the spinal leptomeningeal lesions at the levels of T10 and T11.

Before therapy with bevacizumab, the tumor was microscopically composed of moderately cellular lobules of densely packed tumor cells surrounded by a zone of proliferated capillary-caliber vessels and focal

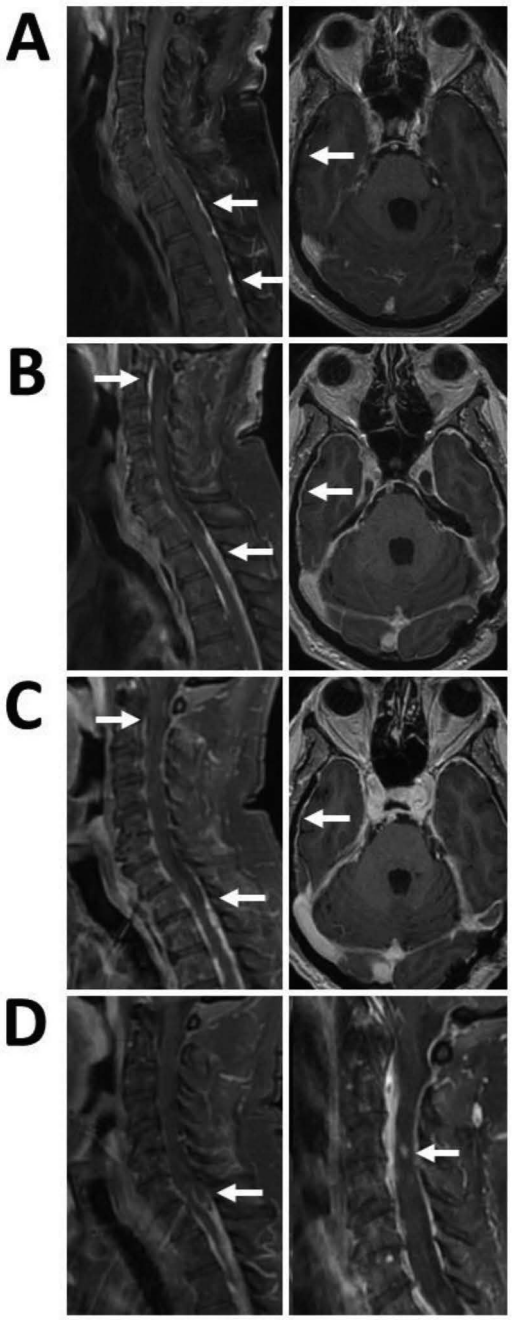

Fig. 1. Radiologic course before and after treatment with bevacizumab. Spinal (left, **A–D**) and cranial (right, **A–C**) MRI showing leptomeningeal contrast-enhancing lesions (**A**, arrows) which progressed over a period of 4 months (**B**). Durable stable disease was observed for up to 12 months after initial treatment with bevacizumab (**C**). The pattern of progression included progressive cystic leptomeningeal tumor (**D**, left, white arrow) and an intramedullary lesion (**D**, right, white arrow).

stromal fibrosis (fig. 2A, B). Cytoplasmic vacuolation was inconspicuous and reticulin staining was sparse. Mitotic activity or necrosis was not observed. Dural tissue was not present in the specimen. Immunohistochemical preparations revealed patchy inhibin α-positive tumor cells (fig. 2C). The differential diagnosis of a metastatic renal tumor was excluded by negative staining for pancytokeratin and renal cell carcinoma (RCC) antibody, and glial neoplasms by negative staining for glial fibrillary acidic protein (GFAP). The Ki-67 proliferation marker labeled around 3% (n = 860 cells) of the tumor cells (fig. 2D).

The biopsy after bevacizumab treatment was performed at the levels of C7 and Th3. Tissue specimens consisted of multiple fragments of dura infiltrated by tumor. The vessels appeared markedly hyalinized and thickened. Interestingly, the tumor cell density was strikingly decreased after treatment with bevacizumab (fig. 2E). The preserved vascular structures in relation to relatively reduced numbers of tumor cells were confirmed via CD31 staining (fig. 2F). The reticulin scaffolding appeared denser, likely reflecting increased vessel-associated reticulin fibers rather than stromal cell-associated fibers. Similar to the initial biopsy, there was no evidence of mitotic activity or necrosis. Only minimal immunolabeling with neuron-specific enolase (NSE; data not shown) and inhibin was seen (fig. 2G). Despite the relative paucity of stromal cells, the proliferative index was high at 20% (n = 134 cells) (fig. 2H).

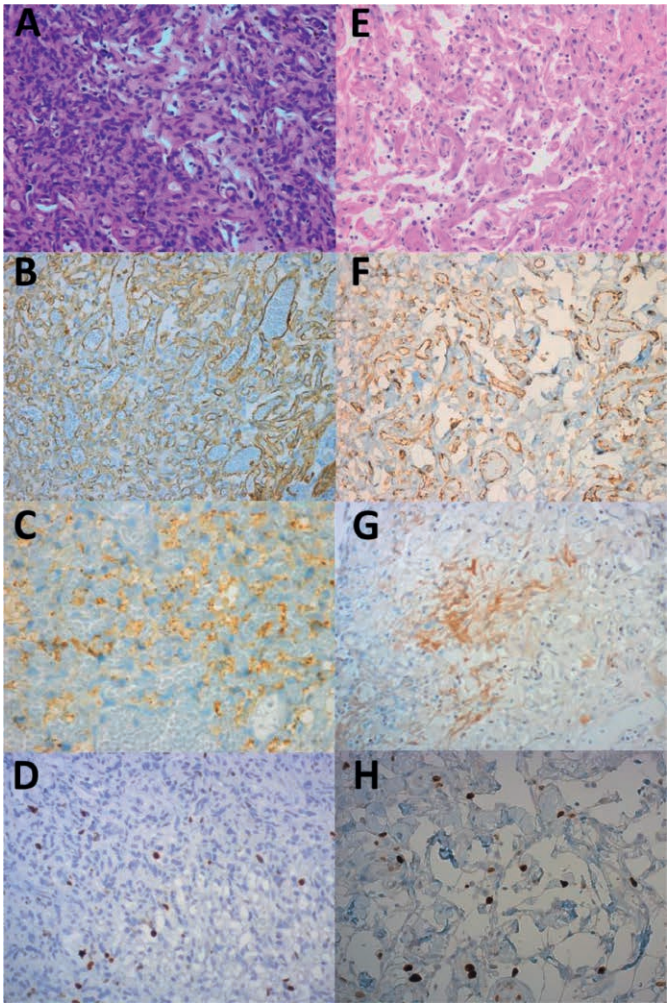

Fig. 2. Histologic changes after therapy with bevacizumab. Hematoxylin-eosin- (**A**, **E**), CD31- (**B**, **F**), inhibin- (**C**, **G**) and Ki-67-stained (**D**, **H**) tissue specimens at 200 × magnification before (left) and after (right) bevacizumab therapy. The initial biopsy featured a compact mixture of generally uniform stromal tumor cells and capillary-caliber vessels (**A**, **B**). After bevacizumab therapy, the stromal tumor cell density appears markedly reduced, while the vessels appear thickened and hyalinized, yet relatively preserved (**E**, **F**). Inhibin-positive stromal cells are seen in the first biopsy (**C**) and within infiltrated dura in the tissue from the second surgery (**G**). Despite the high cellularity, the Ki-67 staining was low at diagnosis (3%, n = 860 cells; **D**). The proliferative index in the second sample was high (20%, n = 134 cells; **H**).

Discussion

This is the first study documenting the histologic findings in a patient with multifocal hemangioblastoma before and after antiangiogenic therapy. Recently, VEGF-based antiangiogenic therapy has entered clinical practice in selected cases of hemangioblastoma [6–8]. However, these studies mainly show disease stabilization, while radiologic response has been described in only 1 case of bevacizumab-treated hemangioblastoma [7]. Currently, there are no reports delineating the radiologic or histologic patterns of response after therapy. In our patient, despite an increased proliferation index, the tumor cell density was decreased after anti-VEGF treatment and vascular structures appeared predominant. Persistent tumor vasculature accompanied with a relatively reduced tumor cell density in a tissue sample obtained from a radiologically progressive tumor could be interpreted as a sign of VEGF-independent angiogenesis. Escape mechanisms from antiangiogenic therapy via up-regulation of non-VEGF proangiogenic signaling, e.g. via angiopoietins, fibroblast growth factors, or placental growth factor, have been proposed in preclinical and clinical models [9].

On the other hand, a diffuse infiltrative pattern of hemangioblastoma cells within the adjacent dura was seen after therapy. This observation may in part be dependent on the biopsy site and extent of sampling. However, the biopsy site of the second intervention was in a region of radiographic progression and therefore presumably represents bevacizumab-resistant tumor. Additionally, the radiologic pattern of progression in this patient with the development of an intramedullary lesion may be interpreted in the context of increased invasiveness of the tumor after antiangiogenic therapy. In other tumor entities, especially glioblastoma, increased tumor invasiveness is thought to represent a possible escape mechanism after antiangiogenic therapy [10, 11].

In conclusion, VEGF-targeting antiangiogenic therapy in cases of hemangioblastoma may involve VEGF-independent angiogenesis via other proangiogenic pathways promoting tumor growth and tumor invasiveness. Further investigation is needed to evaluate the underlying mechanisms of response and escape from antiangiogenic therapy in hemangioblastoma.

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Disclosure Statement

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